

DTIC FILE COPY

AD _____

NATURAL HISTORY OF HTLV III INFECTION IN USAF PERSONNEL:
CLINICAL EVALUATION, LABORATORY EVALUATION,
ASSESSMENT OF IN VIVO AND IN VITRO IMMUNOLOGIC STATUS
AND DATA STORAGE

AD-A226 591

ANNUAL REPORT

R. NEAL BOSWELL

JUNE 1990

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. 86MM6508

Wilford Hall USAF Medical Center
Lackland AFB, Texas 78236-5300

Approved for public release; distribution unlimited

The findings in this report are not to be construed as an
official Department of the Army position unless so designated
by other authorized documents.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited		
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S)			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION Wilford Hall USAF Medical Center		6b. OFFICE SYMBOL (if applicable)	7a. NAME OF MONITORING ORGANIZATION		
6c. ADDRESS (City, State, and ZIP Code) Lackland AFB, Texas 78236-5300			7b. ADDRESS (City, State, and ZIP Code)		
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Research & Development Command		8b. OFFICE SYMBOL (if applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER 86MM6508		
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21701-5012			10. SOURCE OF FUNDING NUMBERS		
			PROGRAM ELEMENT NO. 63105A	PROJECT NO. 3M2- 63105DH29 ✓	TASK NO. AA
11. TITLE (Include Security Classification) Natural History of HTLV III Infection in USAF Personnel: Clinical Evaluation, Laboratory Evaluation, Assessment of In Vivo and In Vitro Immunologic Status, and Data Storage					
12. PERSONAL AUTHOR(S) R. Neal Boswell					
13a. TYPE OF REPORT Annual		13b. TIME COVERED FROM 9/15/88 TO 12/31/89		14. DATE OF REPORT (Year, Month, Day) 1990 June	
15. PAGE COUNT					
16. SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	HTLV III/HIV natural history, HIV disease progression, USAF active duty military HIV, HIV neurological disease, RA 1, prognostic markers of disease progression, sensory-neural		
06	03				
06	13				
19. ABSTRACT (Continue on reverse if necessary and identify by block number)					
<p>The Wilford Hall USAF Medical Center HIV Scientific Group has continued to enroll new HIV positive patients and during the period of this report has reached accumulative number of 989 patients in the databank. Over the last 6 months, we have performed 236 evaluations including 59 new patients and 177 re-evaluations.</p> <p>During the time period of this report, the US Air Force HIV Natural History Study was continued with a significant number of individuals returning for their third evaluation. Rates of progression continued to be low in Walter Reed stage 1 and 2 and much higher in Walter Reed stage 4 and 5. A subgroup of 26 rapid progressors was compared to a controlled population of 26 non progressors and analyzed for surrogate markers of disease progression. Absolute CD4A cell count and serum IgA were the 2 strongest predictors of progression prospectively.</p>					
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT <input type="checkbox"/> UNCLASSIFIED/UNLIMITED <input checked="" type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Mary Frances Bostian			22b. TELEPHONE (Include Area Code) 301-663-7325		22c. OFFICE SYMBOL SGRD-RMI-S

Opportunistic infections were monitored and over 100 were diagnosed. The majority of these, approximately 60%, were Pneumocystis carinii pneumonia. Opportunistic infections were almost never seen when the CD4A helper cell count was greater than or equal to 200. During the period of this report, routine treatment of individuals with CD4A helper cells of below 200 per cubic millimeter with AZT and anti PCP prophylaxis were initiated. The neurological natural history study continued to be productive with extended longitudinal followup of neuropsychiatric and neurological functional parameters being gathered. Routine CSF analysis was terminated during this study. A very fruitful collaboration with investigators in the Cellular-Immunology Lab of Dr Gene Shearer at the National Cancer Institute continued further defining functional perturbations of immune function secondary to HIV infection. A wide variety of intra and extramural collaborations were accomplished. During this transition year, extensive planning and implementation occurred while the Henry M. Jackson Foundation for Military Medical Science replaced the US Army Medical Research and Development Command as the prime funder of HIV research at WHMC. Wilford Hall now functions as an intergrade member of the HMJF Tri-Service ID program with standardization and approval of Walter Reed Retrovirology Research protocols at Wilford Hall, submission of Wilford Hall protocols to the Jackson Foundation for approval and inclusion of Wilford Hall in the GP160 recombinant peptide vaccine trial.

A-1



Significant scientific observations include continued followup of the HIV Natural History Study documenting significant rates of progression over the 12 month time period from Walter Reed stage 1 or 2 to higher stages. In addition, it appears that an increasing Walter Reed stages the rate of progression increases. We have looked at markers of disease progression in the Natural History Study which include extensive immunological and neurological testing. We have identified a cohort of 26 rapid progressors and matched them with a control population of 26 patients who did not progress for CD4 initial T-cell count, race, age and sex. Laboratory markers which distinguished progressors from non-progressors include serum LDH, which was higher in progressors at initial admission, $p=.02$, serum IgA concentration, $p=.001$. Initial IgE values, hemoglobin and platelet counts. Syphilis and hepatitis B serologies were not predictive of progression. The change in serum IgE during the interval trended toward significance $p=.06$. In addition, very recently we have begun performing in-house assays for serum neopterin, TNF/cachectin and beta 2 microglobulin which in other cohort studies have been independent predictors of disease progression.

Our large neurological Natural History Study has continued on all active duty HIV seropositive individuals who received a full neurological evaluation, neuropsychiatric testing and psychiatric evaluation with each evaluation. During this calendar year, routine CSF testing was deemed not to be clinically productive and was dropped from routine laboratory test. CSF data has been derived from this project which have shown that abnormalities are present at all stages of HIV infection to include mild pleocytosis, increased IgG synthesis, elevated proteins and presence of oligoclonal bands. Intensive evaluation of cognitive function in HIV infected individuals has continued to demonstrate that early health related anxiety may adversely effect neuropsychiatric testing, that when patients return for their second and third re-evaluations, while in early stages of disease, they do not show evidence of clinically significant neuropsychiatric impairment and that individuals do show changes with a decrement in neuropsychiatric testing as they progress from HIV asymptomatic to symptomatic disease and into frank AIDS. Studies involving nerve conduction velocity have demonstrated a progressive decline in parameters associated with decline in CD4 counts in HIV infected individuals. However, in early stages this is not clinically significant.

Finally, analysis of opportunistic infections has shown that these are very rare when CD4 counts are greater than or equal to 200 per cubic millimeter. Demographic characteristics in our cohort have tended to follow the same patterns as previously established with approximately with 50% caucasians, 40% blacks and 10% other racial and ethnic groups.

1989 was largely a year of transition for the HIV project at WHMC as US Army funding mechanisms changed but monies were made available to ensure continuity of the project until such time as the Henry M. Jackson Foundation memorandum of understanding was completed between the US Air Force, US Army and all other principals.

Close interactions among multidisciplinary groups in comparing natural history data, CD4 cell counts, neuropsychiatric testing, neurological findings, pediatric HIV infections, spouse studies and many other US Army RV protocols were reviewed, accepted and principal investigators designated at Wilford Hall USAF Medical Center.

During this time period, funding largely fulfilled the function of keeping the HIV natural history study alive until such time as the Henry M. Jackson Foundation for military medical science could undertake the funding and administration of this research in collaboration with the Tri-service HIV project with the US Army as lead agency for infectious disease research.

1. Clerici M, Stocks N, Zajac R, Boswell R, Via C, Shearer G. Circumvention of Defective CD4 T Helper Cell Function in HIV Infected Individuals by Stimulation with HLA Alloantigens. *Journal of Immunology*, Vol 144, 3266-3271, 1990.
2. Goethe K, Mitchell J, Marshall D, Brey R, Cahill W, Leger G, Hoy L, Boswell R. Neuropsychological and Neurological Function of Human Deficiency Virus Seropositive Asymptomatic Individuals. *Arch of Neurol*, Vol 46:129-133, 1989.
3. Brey R, Houk R, Patel P, Boswell R, et al. Anticardiolipin Antibody and HIV Infection. *Clinical Exp Rheum* 88, 6:199, 1988.
4. Arroyo R, Brey R, Higgs J, Boswell R. Anticardiolipin Antibody in Patients with HIV Infection. Submitted for Publication.
5. Ridley D, Houk R, Reid M, Boswell R. Early Lymphocyte Transformation Abnormalities in Human Immunodeficiency Virus Infection. *J Clin Immunology* Vol 9:2, 119, 124, 1989.
6. Clerici M, Stocks N, Zajac R, Boswell R, Bernstein D, Mann D, Shearer G, Berzofsky J. IL-2 Production Permits Detection of Antigenic Peptide Recognition by T Helper Lymphocytes from Asymptomatic HIV Seropositive Individuals. *Nature*, Vol 339, 383-385, 1989.
7. Lucey D, Zajac R, Melcher G, Butzin C, Boswell R. Comparison of IgE levels and CD+4 T Cell Counts in 662 HIV Positive USAF personnel. *AIDS Research and Human Retroviruses*, Vol 6, 427-429, 1990.
8. Golding H, Shearer G, Hillman K, Lucas P, Manischewitz J, Zajac R, Clerici M, Gress R, Boswell R, Golding B. Common Epitope in HIV-1, GP41 and HLA Class I Elicits Immunosuppressive Autoantibodies Capable of Contributing to Immune Dysfunction in HIV-1 Infected Individuals. *J Clin Invest*, 83: 1430-1435, 1989.
9. Warren R, Wolf H, Shuler K, Eichberg J, Zajac R, Boswell R, Kanda P, Kennedy R. Synthetic Peptides Define the Fine Specificity of HIV gp160 Humoral Immune Response in HIV-1 Infected Chimpanzees. *Journal of Virology* 64: 486-492, 1990.
10. Putney S, LaRosa G, Matthews T, Emini E, Boswell R, Bolognesi D, Weinhold K. The Principal Neutralizing Determinant of HIV-1. *Proceedings of the HIV Annual Cent Gardes Meeting*, Paris, France, 1989.
11. Clerici M, Stocks N, Zajac R, Boswell R, Lucey D, Via C, Shearer G. Detection
12. Fuchs D, Shearer G, Boswell R, Clerici M, Reibnegger G, Werner E, Zajac R, Wachter H. Increased Serum Neopterin in Patients with HIV-1 Infection Correlates to Reduced in Vitro IL-2 Production. *Clin Exp Immunol*, 80, 44-48, 1990.
13. Clerici M, Stocks N, Zajac R, Boswell R, Shearer G. Accessory Cell Function in Asymptomatic Human Immunodeficiency Virus-Infected Patients. *Clinical Immunology and Immunopathology*, Vol 54:168-173, 1990.

14. Lucey R, Hensley R, Butzin C, Boswell R. Early Upregulation and Late Decline in CD₄ Monocytes with HIV Infection. Presented at the 32nd Annual Air Force Regional Meeting of the American College of Physicians, San Antonio, Texas, March 1990. Submitted for Publication.
15. Mitchell J, Marshall D, Goethe E, Leger D, Boswell R. Human Immunodeficiency Virus (HIV): Immune System Compromised and Neuropsychological Functioning. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989.
16. Mitchell J, Marshall D, Leger D, Boswell R. Longitudinal Neuropsychological Evaluations on a Cohort of HIV Infected USAF Personnel. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989 and V Int Conference on AIDS, Montreal, Canada, June, 1989.
17. Arroyo R, Brey R, Higgs J, Boswell R, Harris N. Anticardiolipin Antibody in Patients with HIV Infection. Presented at the V Int Conference on AIDS, Montreal Canada, June 1989.
18. Andrzejewski C, Benton J, Valtier S, Lucey D, Boswell N. Autoreactivity in Patients Infected with HIV. Presented at the V Int Conference on AIDS, Montreal, Canada, 1989.
19. Lucey D, Zajac R, Melcher G, Butzin C, Boswell R. Serum IgE levels vary with Absolute CD4A Lymphocyte Counts in HIV Positive Persons. Presented at the V International Conference on AIDS, Montreal, Canada, June 1989.
20. Lucey D, Zajac R, Melcher G, Butzin C, Boswell R. Comparison of IgE Levels and CD4 T-Cell Counts in 22 HIV-Positive US Air Force Personnel. Presented at 29th ICAAC, Houston, Texas, October 1989.
21. Lucey D, Melcher G, Zajac R, Butzin A, Boswell R. Markers of Disease Progression in the USAF HIV Natural History Study. Presented at 29th ICAAC, Houston, Texas, October 1989.
22. Lucey D, Hensley R, Butzin C, Boswell R. Selection Depletion of CD4+ Monocytes During HIV Disease. Presented at 29th ICAAC, Houston, Texas, October 1989.
23. Shearer G, Clerici M, Stocks N, Zajac R, Boswell R, Via C. Bypass of Defective CD4 T-Helper Cell Function in HIV+ Individuals by Stimulation with Alloantigens. Presented at FASEB, Washington, DC, May 1989.
24. Clerici M, Shearer G, Stocks N, Zajac R, Boswell R, Via C. Defective T-Helper Pathways in Asymptomatic HIV+ Individuals. Presented at FASEB, Washington, DC, May 1989.
25. Clerici M, Stocks N, Zajac R, Boswell R, Shearer G, Berzofsky J. T-Helper Cell Response to Synthetic HIV Peptide Antigens in Asymptomatic HIV Seropositive Individuals. Presented at FASEB, Washington, DC, May 1989.
26. Lucey D, Zajac R, Melcher G, Butzin C, Boswell R. Serum IgE Levels Vary with Absolute CD4A Lymphocyte Counts in HIV Positive Persons. Presented at the V International Conference on AIDS, Montreal, Canada, June 1989.
27. Brey R, Arroyo R, Marshall D, Boswell R. Intrathecal Production of Anticardiolipin Antibodies in HIV-1 Infection. Presented at the V Int Conference on AIDS Montreal, Canada, June 1989.

28. Clerici M, Stocks N, Zajac R, Boswell R, Via C, Shearer G. Circumvention of Defective CD4 T-Helper Cell Function in HIV+ Individuals by Stimulation with HLA Alloantigens. Presented at FASEB 1989.
29. Gronseth G, Marshall D, Brey R, Lucey D, Boswell R. Aids Dementia Complex (ADC) in the Population Based USAF HIV Study. Presented at the 31st Annual Air Force Regional Meeting of the American College of Physicians, Bethesda, Mar 89.
30. Marshall D, Lucey D, Zajac R, Brey R, Boswell N. Prevalence of CNS Opportunistic Infection (OI) in USAF Epidemiologic Study of HIV Infection. Presented at the 31st Annual Air Force Regional Meeting of the American College of Physicians, Bethesda, Maryland, Mar 89.
31. Freeman T, Hensley R, Butzin C, Boswell N. Activated T-cells and Human Immunodeficiency Virus (HIV) Progression. Presented at the 31st Annual Air Force Regional Meeting of the American College of Physicians, Bethesda, Maryland, 1989.
32. Zajac R, Lucey D, Melcher G, Mumm A, Gibson R, Marshall D, Boswell R. HIV in the USAF-1989. Presented at the 31st Annual Air Force Regional Meeting of the American College of Physicians, Bethesda, Maryland, Mar 89.
33. Benton J, Ward W, Boswell R, Zajac R. Evaluation of HIV Core Antigen Tests. Presented at the 14th Annual Meeting of the Society of Armed Forces Medical Laboratory Scientists. San Antonio, Texas, March 89.
34. Freeman T, Hensley R, Butzin C, Boswell R. Activation of T-cells and HIV Progression. Presented at 31st Annual Air Force Regional Meeting of the American College of Physicians, Bethesda, Maryland, March 1989.
35. Brey R, Arroyo R, Marshall D, Boswell R. Anticardiolipin Antibodies in the Cerebrospinal Fluid of HIV Infected Patients. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989.
36. Marshall D, Lucey D, Zajac R, Brey R, Boswell R. Prevalence of CNS opportunistic Infection (OI) in the USAF Epidemiologic Study of HIV Infection. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989.
37. Marshall D, Brey R, Butzin C, Zajac R, Boswell R. Longitudinal CSF Findings in 240 HIV-Infected USAF Personnel. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989.
38. Marshall D, Brey R, Butzin C, Zajac C, Boswell R. Formulas for Intrathecal Production of IgG in the Setting of HIV Infection. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989.
39. Marshall D, Butzin C, Brey R, Boswell R. Integrity of the Blood-Brain-Barrier (BBB) During the Course of HIV-1 Infection. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989.
40. Marshall D, Gronseth G, Brey B, Lucey D, Boswell R. AIDS Dementia Complex (ADC) in the Population Based USAF HIV Study. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989.
41. Mitchell J, Marshall D, LeForce B, Leger D, Boswell R. Accuracy of the Mini Mental State Examination (MMSE) for Screening of Neuropsychological Impairment in Human Immunodeficiency Virus (HIV) - Infected Patients. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989.

42. Mitchell J, Marshall D, Goethe E, Leger D, Boswell R. Human Immunodeficiency Virus (HIV): Immune System Compromised and Neuropsychological Functioning. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989.
43. Mitchell J, Marshall D, Leger D, Boswell R. Longitudinal Neuropsychological Evaluations on a Cohort of HIV Infected USAF Personnel. Presented at the American Academy of Neurology Annual Meeting, Cincinnati, Ohio, April 1989 and V Int Conference on AIDS, Montreal, Canada, June, 1989.
44. Arroyo R, Brey R, Higgs J, Boswell R, Harris N. Anticardiolipin Antibody in Patients with HIV Infection. Presented at the V Int Conference on AIDS, Montreal Canada, June 1989.
45. Andrzejewski C, Benton J, Valtier S, Lucey D, Boswell N. Autoreactivity in Patients Infected with HIV. Presented at the V Int Conference on AIDS, Montreal, Canada, 1989.
46. Lucey D, Zajac R, Melcher G, Butzin C, Boswell R. Serum IgE levels vary with Absolute CD4+ Lymphocyte Counts in HIV Positive Persons. Presented at the V International Conference on AIDS, Montreal, Canada, June 1989.
47. Lucey D, Zajac R, Melcher G, Butzin C, Boswell R. Comparison of IgE Levels and CD4+ T-Cell Counts in 22 HIV-Positive US Air Force Personnel. Presented at 29th ICAAC, Houston, Texas, October 1989.
48. Lucey D, Melcher G, Zajac R, Butzin A, Boswell R. Markers of Disease Progression in the USAF HIV Natural History Study. Presented at 29th ICAAC, Houston, Texas, October 1989.
49. Lucey D, Hensley R, Butzin C, Boswell R. Selection Depletion of CD4+ Monocytes During HIV Disease. Presented at 29th ICAAC, Houston, Texas, October 1989.
50. Shearer G, Clerici M, Stocks N, Zajac R, Boswell R, Via C. Bypass of Defective CD4 T-Helper Cell Function in HIV+ Individuals by Stimulation with Alloantigens. Presented at FASEB, Washington, DC, May 1989.
51. Clerici M, Shearer G, Stocks N, Zajac R, Boswell R, Via C. Defective T-Helper Pathways in Asymptomatic HIV+ Individuals. Presented at FASEB, Washington, DC, May 1989.
52. Clerici M, Stocks N, Zajac R, Boswell R, Shearer G, Berzofsky J. T-Helper Cell Response to Synthetic HIV Peptide Antigens in Asymptomatic HIV Seropositive Individuals. Presented at FASEB, Washington, DC, May 1989.
53. Lucey D, Zajac R, Melcher G, Butzin C, Boswell R. Serum IgE Levels Vary with Absolute CD4+ Lymphocyte Counts in HIV Positive Persons. Presented at the V International Conference on AIDS, Montreal, Canada, June 1989.
54. Brey R, Arroyo R, Marshall D, Boswell R. Intrathecal Production of Anticardiolipin Antibodies in HIV-1 Infection. Presented at the V Int Conference on AIDS Montreal, Canada, June 1989.
55. Clerici M, Stocks N, Zajac R, Boswell R, Via C, Shearer G. Circumvention of Defective CD4 T-Helper Cell Function in HIV+ Individuals by Stimulation with HLA Alloantigens. Presented at FASEB 1989.

56. Lucey R, Melcher G, Zajac R, Benton J, Butzin C, Boswell R. Predictors of HIV Disease Progression in Personnel with Three WIMC Evaluations. Presented at the 32nd Annual Air Force Regional Meeting of the American College of Physicians, San Antonio, Texas, March 1990.
57. Spencer G, Melcher G, Zajac R, Boswell R. T4 lymphocyte count and AIDS-Defining Opportunistic Infections. Presented at the 32nd Annual Air Force Regional Meeting of the American College of Physicians, San Antonio, Texas, March 1990.
58. Zajac R, Lucey D, Melcher G, Jaso R, Abbadessa S, Fowler C, Hall K, Boswell R. Oral hairy leukoplakia (OHL) in the USAF HIV Natural History Cohort. Presented at the 32nd Annual Air Force Regional Meeting of the American College of Physicians, San Antonio, Texas, March 1990.
59. Zajac R, Lucey D, Jaso R, Melcher G, Abbadessa S, Fowler C, Reed K, Sumaya C, Butzin C, Hall K, Boswell R. Oral Hairy Leukoplakia (OHL) in the USAF HIV Natural History Study Cohort. Presented at 29th ICAAC, Houston, Texas, October 1989.
60. Rundell J, Wise M, Brown G, Holloway H, Boswell R, Weiss T. Relative Frequency of HIV Disease as a Cause of Mood Disorders in a General Hospital. Presented at the Neuropsych Conference VI International Conference on AIDS, Monterey, California, June 1990.
61. Rundell J, Praus D, Thomason J, Brown G, Marshall D, Holloway H, Boswell R. CSF Findings and Request for Psychiatric Examinations in HIV-Infected Patients. Presented at the Neuropsych Conference VI International Conference on AIDS, Monterey, California, June 1990.
62. Rundell J, Praus D, Brown G, Marshall D, Boswell R, Holloway H. CSF Parameters, Immune Status, Serum Viral Titers, Anxiety, and Depression in HIV Disease. Presented at the Neuropsych Conference VI International Conference on AIDS, Monterey, California, June 1990.
63. Lucey D, Hendrix C, Andrzejewski C, Melcher G, Zajac R, Boswell R. Hepatitis C in the United States Air Force Immunodeficiency Virus Positive Cohort. Presented at the VI International Conference on AIDS, San Francisco, California, June 1990.